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EXAMINER	
DANG, IAN D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,802	ALITALO, KARI	
	Examiner	Art Unit	
	IAN DANG	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46,48,62-64,67-70,72-75 and 77-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,48,62-64,67-70,72-75 and 77-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 09 December 2008 has been entered in full. Claims 1-45, 47, 49-61, 65-66, 71, and 76 have been cancelled and claims 62, 63, 67, 68, and 77 have been amended.

Claims 46, 48, 62-64, 67-70, 72-75, 77-98 are under examination.

Specification

The objection to the specification is withdrawn because Applicants have provided a new title for the instant application.

Rejection Withdrawn

35 USC § 112, Second paragraph

Applicant's amendment made to claims 68 and 77 by changing the dependency of claims 68 and 77 filed 12/09/2008 have overcome the rejection of claims 68-70 and 77 under 35 U.S.C. 112, second paragraph. The rejection of claims 68-70 and 77 under 35 U.S.C. 112, second paragraph, is withdrawn

New Grounds of Rejection

Claim Rejections - 35 USC § 112, Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46, 48, 62-64, 67-70, 72-75, 77-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 46, 69, 74, and 79 use acronyms without first defining what they represent in the independent claims (see for example, “PAL-E”). While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

Claims 46, 62, 67, 72, 73, 78, 81, 82, 85, 86, 89, 90, 91, 92, and 94 are indefinite because these claims are missing steps and limitations. Please note that the recitation of claims 46 and 62 reciting "an effective amount" and, claim 62 including a conclusion reciting, e.g., "where the inhibition of Flt4 function treats breast cancer" would overcome the rejection.

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 46, 48, 62-64, 67, 68-70, 72, 73, 74, 75, 78, 79, 80, 81, 83, 84, 85, 86, 87, 88, 90, 91, 92, 94-96 are rejected under double patenting over claims 1, 6, 17, 32, 38, 50-52, and 53 of US Patent 6,824,777.

Although the Examiner has previously indicated that claims 46, 62, 67, 72-75 and 78-98 are allowable in the office action mailed October 16, 2008, the Examiner has reconsidered its position regarding the allowability of these claims and has again rejected them under double patenting over claims 1, 17, 32, 38, 50-52, and 53 of US Patent 6,824,777. The scope of claims 46, 62-64, 67, 72, 73, 78, 81, 83, 84, 85, 86, 90, 91, 92, 94-96 of the instant application is encompassed by the one of claims 1, 17, 32, 38, 50-52, and 53 of the '777 patent. In view of the specification of the '777 patent, the subject matter patented in claims 1, 17, 32, 38, 50-52, and 53 of the '777 patent include the subject matter recited in claims 46, 62-64, 67, 72, 73, 78, 81, 83, 84, 85, 86, 90, 91, 92, 94-96 of the instant specification.

Claim 46 is drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease, comprising administering to said mammalian organism a composition, wherein said neoplastic disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells, wherein said composition comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vascular endothelial cells of said organism, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 1 of the '777 patent is drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 1 of the '777** patent does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 46** of this instant application and **claim 1 of the '777** patent are not patentably distinct because **claim 5 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) in combination with **claim 1 of the '777** encompass the limitations of **claim 46** of the instant application.

In addition, **claim 48** of the instant application is drawn to an inhibitor further comprises an anti-neoplastic agent conjugated to a bispecific antibody or fragment thereof matching the limitations of **claim 6 of the '777 patent**.

Claim 62 of the instant application is drawn to a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising administering to said mammal a composition, said composition comprising an

inhibitor of binding of an Flt4 ligand protein to Flt4 expressed in cells of said mammal, thereby inhibiting Flt4 function, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 32 of the '777 patent is drawn to a method of treating a mammal having breast cancer characterized by endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; and (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

Although **claim 32 of the '777** patent does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 62** of this instant application and **claim 32 of the '777** patent are not patentably distinct because **claim 35 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) in combination with **claim 32 of the '777 patent** encompass the limitations of **claim 62** of the instant application.

In addition, **claim 63** of the instant application is drawn to a mammal that is a human matching the limitations of **claim 33 of the '777 patent**.

Finally, **claim 64** of the instant application is drawn to a screening step preceding the administering step matching the limitations of **claim 34 of the '777**.

Claim 67 is drawn to a method for treating a neoplastic disorder in a human subject, comprising: (a) screening a human subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and
(b) administering a composition to a human subject identified according to (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, to inhibit Flt4 mediated proliferation of said Flt4-expressing cells, wherein the composition comprises a means for inhibiting Flt4 function in mixture with a pharmaceutically acceptable diluent, adjuvant, or carrier, wherein the means for inhibiting comprises a member selected from the group consisting of: (a) an anti-Fit4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Fit4 antibody; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody; (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro- VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

Claim 53 of the '777 patent is drawn to a method of treating a human having breast cancer characterized by endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said human a composition, said composition comprising an inhibitor of

binding between Flt4 ligand protein and Flt4 expressed in cells of said human, thereby inhibiting Flt4 function, wherein the inhibitor comprises a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

Although **claim 53 of the '777 patent** does not recite a method for treating a neoplastic disorder in a human subject, **claim 67** of this instant application and **claim 53 of the '777** patent are not patentably distinct because the specification of the '777 patent teaches that the method includes a method of treating a mammalian organism suffering from a neoplastic disease characterized by expression of Flt4 in vascular endothelial cells (column 9, lines 7-10) **and breast cancer is a neoplastic disease** encompassing the limitations of **claim 67** of the instant application.

In addition, although **claim 53 of the '777 patent** does not include the inhibitor comprising (a) an anti-Fit4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Fit4 antibody; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody; (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21), the inhibitors of **claim 53 of the '777 patent** include the different inhibitors (a)-(d) because the specification of the '777 patent contemplates using these inhibitors (column 8, lines 34-50) meeting the limitation of **claim 67** of the instant application.

Futhermore, the inhibitors of **claim 53 of the '777 patent** includes a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen is selected from the group consisting of PAL-

E , VEGFR-1, VEGFR-2, and an inhibitor further comprises an anti-neoplastic agent conjugated to a bispecific antibody or fragment thereof,

Claims 68 and 70 of this instant application and **claim 53 of the '777** patent are not patentably distinct because **claim 5 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) and **claim 6 of the '777 patent** recites an anti-neoplastic agent conjugated to a bispecific antibody or fragment thereof recited in encompass the limitations of **claims 68 and 70** of the instant application.

In addition, the specification of the '777 patent contemplates using the inhibitor bispecific antibody binds to a blood vascular endothelial marker antigen selected from the consisting of PAL-E, VEGFR-1, and VEGFR-2 (column 10, lines 4-6) meeting the limitation of **claim 69** of the instant application.

In addition, **claim 63** of the instant application is drawn to a mammal that is a human matching the limitations of **claim 33 of the '777 patent**.

Moreover, **claim 64** of the instant application is drawn to a screening step preceding the administering step matching the limitations of **claim 34 of the '777**.

Finally, although claim

Claim 72 is drawn to a method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-

mediated proliferation of the blood vessel endothelial cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 38 of the '777 patent is drawn to method of inhibiting proliferation of cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 38 of the '777 patent** does not recite proliferation of blood vessel endothelial cells, **claim 72** of this instant application and **claim 38 of the '777** patent are not patentably distinct because the specification teaches that a preferred embodiment of the invention includes cells from lymphatic or vascular endothelial cells (column 8, line 24 of US Patent 6,824,777) encompassing the limitations of **claim 72** of the instant application.

Although **claim 72 of the '777** patent does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 72** of this instant application and **claim 38 of the '777** patent are not patentably distinct because **claim 41 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) in

combination with **claim 38 of the '777 patent** encompass the limitations of **claim 72** of the instant application.

Claim 73 is drawn to a method of inhibiting proliferation of endothelial cells in a human organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the blood vessel endothelial cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 38 of the '777 patent is drawn to method of inhibiting proliferation of cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 38 of the '777 patent** does not recite proliferation of endothelial cells, **claim 73** of this instant application and **claim 38 of the '777** patent are not patentably distinct because the specification teaches that a preferred embodiment of the invention includes cells

from lymphatic or vascular endothelial cells (column 8, line 24 of US Patent 6,824,777) encompassing the limitations of **claim 73** of the instant application.

Although **claim 73 of the '777** patent does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 73** of this instant application and **claim 38 of the '777** patent are not patentably distinct because **claim 41 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody (column 9, lines 60-67 of US Patent 6,824,777) in combination with **claim 38 of the '777 patent** encompass the limitations of **claim 73** of the instant application.

Claim 74 of this instant application and **claim 6 of the '777 patent** are not patentably distinct because **claim 6 of the '777 patent** recites an anti-neoplastic agent conjugated to a bispecific antibody or fragment thereof recited in encompass the limitations of **claims 74** of the instant application.

In addition, **claim 75** of this instant application **claim 6 of the '777 patent** are not patentably distinct because the specification of the '777 patent contemplates a blood vascular endothelial marker antigen selected from the consisting of PAL-E, VEGFR-1, and VEGFR-2 (column 10, lines 4-6) meeting the limitation of **claim 75** of the instant application.

Claim 78 is drawn to a method of inhibiting proliferation of endothelial cells in a human organism having a breast carcinoma characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells, comprising administering to said human organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody

or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 38 of the '777 patent is drawn to method of inhibiting proliferation of cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 38 of the '777 patent** does not recite proliferation of endothelial cells in a human organism having a breast carcinoma, **claim 78** of this instant application and **claim 38 of the '777** patent are not patentably distinct because the specification teaches that a preferred embodiment of the invention includes cells from lymphatic or vascular endothelial cells (column 8, line 24 of US Patent 6,824,777) and that Flt4 expression occurs in blood vasculature associated with at least some breast cancers (column 8, lines 18-21) encompassing the limitations of **claim 78** of the instant application.

In addition, **claim 79** of this instant application **claim 6 of the '777 patent** are not patentably distinct because the specification of the '777 patent contemplates a blood vascular endothelial marker antigen selected from the consisting of PAL-E, VEGFR-1, and VEGFR-2 (column 10, lines 4-6) meeting the limitation of **claim 79** of the instant application.

Claim 80 of this instant application and **claim 6 of the '777 patent** are not patentably distinct because **claim 6 of the '777 patent** recites an anti-neoplastic agent conjugated to a

bispecific antibody or fragment thereof recited in encompass the limitations of **claim 80** of the instant application.

Although **claim 78 of the '777** patent does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 78** of this instant application and **claim 38 of the '777** patent are not patentably distinct because **claim 41 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody (column 9, lines 60-67 of US Patent 6,824,777) in combination with **claim 38 of the '777 patent** encompass the limitations of **claim 78** of the instant application.

Claim 81 is drawn to a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein the inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; and (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQID NO:21) or human prepro-VEGF-D (SEQID NO:22) conjugated to an antineoplastic agent.

Claim 50 of the '777 patent is drawn a method of inhibiting genesis of lymphatic vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in lymphatic vessels, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody; (b) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (c) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 50 of the '777 patent** does not recite inhibiting genesis of blood, **claim 81** of this instant application and **claim 50 of the '777** patent are not patentably distinct because the specification teaches that a preferred embodiment of the invention includes lymphatic or vascular endothelial cells (column 8, line 24 of US Patent 6,824,777) encompass the limitations of **claim 94** of the instant application.

In addition, although **claim 50 of the '777 patent** does not recite a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQID NO:21) or human prepro-VEGF-D (SEQID NO:22) conjugated to an antineoplastic agent, **claim 81** of this instant application and **claim 50 of the '777 patent** are not patentably distinct the recitation of the specification discloses an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells includes a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQID NO:21) or human prepro-VEGF-D (SEQID NO:22) conjugated to an antineoplastic agent encompass the limitations of **claim 81** of the instant application.

In addition, **claim 83** of the instant application is drawn to a mammal that is a human matching the limitations of **claim 51 of the '777 patent**.

Finally, **claim 84** of the instant application is drawn to a tumor characterized by blood vessels that express Flt4 matching the limitations of **claim 52 of the '777 patent**.

Claim 85 is drawn to a method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, comprising administering to a mammalian organism a composition that comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 receptor tyrosine kinase (Flt4) expressed in cells of said organism, wherein the mammalian organism has a tumor characterized by blood and lymphatic vessels that express Flt4, and wherein the composition inhibits proliferation of the blood and lymphatic vessels, thereby inhibiting growth or metastatic spread of the tumor, wherein the inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; and (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQID NO:21) or human prepro-VEGF-D (SEQID NO:22) conjugated to an antineoplastic agent.

Claim 50 of the '777 patent is drawn a method of inhibiting genesis of lymphatic vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in lymphatic vessels, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody; (b) a polypeptide comprising an antigen binding fragment of an anti

Flt4 antibody; and (c) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 50 of the '777 patent** does not recite a method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, **claim 85** of this instant application and **claim 50 of the '777 patent** are not patentably distinct because **claim 52 of the '777 patent** reciting a cancer characterized by lymph node metastases in combination with **claim 50 of the '777 patent** encompass the limitations of **claim 85** of the instant application.

Claim 86 is drawn to a method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, comprising administering to a mammalian organism a composition that comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 receptor tyrosine kinase (Flt4) expressed in cells of said organism, wherein the mammalian organism has a tumor characterized by blood and lymphatic vessels that express Flt4, and wherein the composition inhibits proliferation of the blood and lymphatic vessels, thereby inhibiting growth or metastatic spread of the tumor, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Although **claim 50** does not recite a method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, claim 86 of this instant application and **claim 50 of the '777 patent** are not patentably distinct because **claim 52 of the '777 patent** reciting a cancer characterized by lymph node metastases in combination with **claim 50 of the '777 patent** encompass the limitations of **claim 86** of the instant application.

In addition, although **claim 50 of the '777 patent** does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds

Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 86** of this instant application and **claim 50 of the '777 patent** are not patentably distinct because the recitation of an anti-Flt4 antibody of in **claim 50 of the '777 patent** encompasses a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen of the instant claims as definted in column 9, lines 60-67 of US Patent 6,824,777 meeting the limitations of **claim 86** of the instant application.

Finally, although **claim 50 of the '777 patent** does not recite a diagnosis step prior to the administering step comprising identifying a patient having a tumor characterized by blood vessels that express Flt4 and identifying a patient having lymph node metastasis of a tumor, **claim 52 of the '777 patent** reciting a cancer characterized by lymph node metastases in combination with **claim 50 of the '777 patent** reciting a method of inhibiting genesis of lymphatic vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in lymphatic vessels inherently encompasses the limitations of **claims 87 and 88** of the instant application.

Claim 90 is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising: (a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and (b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 17 of the '777 patent is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of: (a) screening a mammalian subject to identify a neoplastic disorder characterized by cells expressing Flt4 receptor tyrosine kinase (Flt4); and (b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (i) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (ii) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 17 of the '777 patent** does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 90** of this instant application and **claim 17 of the '777 patent** are not patentably distinct because **claim 23 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) in combination with **claim 17 of the '777 patent** encompass the limitations of **claim 90** of the instant application.

Claim 91 is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising: (a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and (b)

administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody; (ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody (iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and wherein said organism has a neoplastic disorder characterized by blood vessels comprising endothelial cells that express Flt4 matching the limitations of claim 17 of US 6,824,777.

Claim 17 of the '777 patent is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of: (a) screening a mammalian subject to identify a neoplastic disorder characterized by cells expressing Flt4 receptor tyrosine kinase (Flt4); and (b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (i) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (ii) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 17 of the '777 patent** does not recite the inhibitor comprising (ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody, the inhibitors of **claim 17 of the '777 patent** encompass (ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody, **claim 91** of this instant application and **claim 17 of the '777 patent** are not patentably distinct because the antibodies to VEGF-C and VEGF-D or polypeptide comprising an antigen binding fragment to antibodies to VEGF-C and VEGF-D are well known to inhibit proliferation of Flt4-expressing cells.

In addition, although **claim 17 of the '777** does not include the inhibitor comprising (ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody, the anti-VEGF-C antibody and anti-VEGF-D antibody would be an inhibitor of neoplastic cell growth.

Claim 92 is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising: (a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and (b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Claim 17 of the '777 patent is drawn to a method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of: (a) screening a mammalian subject to identify a neoplastic disorder characterized by cells expressing Flt4 receptor tyrosine kinase (Flt4); and (b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of: (i) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (ii) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 17 of the '777 patent** does not recite an inhibitor comprising a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, **claim 92** of this instant application and **claim 17 of the '777 patent** are not patentably distinct because **claim 23 of the '777 patent** recites an anti-Flt4 antibody which is defined as a bispecific antibody or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen (column 9, lines 60-67 of US Patent 6,824,777) in combination with **claim 17** encompass the limitations of **claim 90** of the instant application.

Claim 94 is drawn to a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said

organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

Claim 50 of the '777 patent is drawn to a method of inhibiting genesis of lymphatic vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in lymphatic vessels, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a member selected from the group consisting of: (a) an anti-Flt4 antibody; (b) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and (c) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

Although **claim 50 of the '777 patent** does not recite inhibiting genesis of blood, claim 90 of this instant application and **claim 50 of the '777 patent** are not patentably distinct because the specification teaches that a preferred embodiment of the invention includes lymphatic or vascular endothelial cells (column 8, line 24 of US Patent 6,824,777) encompass the limitations of **claim 94** of the instant application.

In addition, **claim 95** of the instant application is drawn to a mammal that is a human matching the limitations of **claim 51 of the '777 patent**.

Finally, **claim 96** of the instant application is drawn to a tumor characterized by blood vessels that express Flt4 matching the limitations of **claim 52 of the '777 patent**.

Conclusion

Claims 46, 48, 62-64, 67, 68-70, 72, 73, 74, 75, 78, 79, 80, 81, 83, 84, 85, 86, 87, 88, 90, 91, 92, 94-96 are rejected. Claims 77, 93, and 97-98 are objected because they depend on rejected claims.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IAN DANG whose telephone number is (571)272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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